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Previews

Gut microbiota: Guardians of the female gut health

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The role of gut microbiota and their sex-specific differences in colorectal cancer remain to be explored. In the current issue of *Cancer Cell*, Li et al. discovered that estrogen facilitates the colonization of *Carnobacterium maltaromaticum* in the mouse gut and exerts its anti-colorectal cancer effects by increasing the production of vitamin D3.

Globally, the incidence and mortality risks of colorectal cancer (CRC) are lower in females compared with males.[1] Clinical studies have found a negative correlation between endogenous estrogen levels and the risk of CRC in postmenopausal women.[2] Estrogen replacement therapy and reproductive history have been shown to reduce the CRC risk in postmenopausal women.[3,4] These various studies suggest that estrogen is an important protective factor against CRC. Although previous mechanistic reports have indicated that estrogen can inhibit the progression of CRC by activating estrogen receptors[5] and that estrogen levels may influence gut microbiota,[6] it is still unknown whether estrogen affects the occurrence of CRC through modulation of the gut microbiota. In the current issue of *Cancer Cell*, Li et al. investigate a gender-specific bacterium, *Carnobacterium maltaromaticum* (*C. maltaromaticum*), which is enriched in the female, and elucidate its role in exerting anti-CRC effects (Figure 1).[7]

To investigate why the risk of CRC is lower in females, the authors first hypothesized the presence of a certain anti-cancer bacterium in the healthy female gut, which is depleted in female patients with CRC. The authors performed a comparison of gut microbiota profiles between female patients with CRC and healthy females. They discovered a notable decrease in *C. maltaromaticum* among female patients with CRC, whereas no difference was observed among male patients. Additionally, *C. maltaromaticum* was enriched in the females than the males, suggesting that *C. maltaromaticum* may be a gender-specific anti-CRC bacterium.

Next, in mouse models of CRC, including $Apc^{Min/+}$ mice and azoxymethane/dextran sodium sulfate mice, oral administration of *C. maltaromaticum* reduced tumor burden in female mice with colon neoplasms. However, in ovariectomized female mice, the protective effect of *C. maltaromaticum* against CRC was abolished. Conversely, the introduction of *C. maltaromaticum* did not result in a reduction of tumor burden in male mice. However, when the male mice underwent castration and received estrogen supplementation, the protective effect of *C. maltaromaticum* against CRC was reinstated. In investigating the specific mechanisms behind these findings, the authors addressed two scientific questions: "Why is *C. maltaromaticum* enriched in the female gut?" and "How does *C. maltaromaticum* exert its protective effect against CRC?" To understand why *C. maltaromaticum* is enriched in the female gut, the researchers performed biotinylation-based far-western and pull-down assays. These assays revealed that the gender-specific transmembrane protein SLC3A2, located on the colonic epithelial cells, interacts with the DDCPase present on the cell membrane of *C. maltaromaticum*. Additionally, estrogen was found to activate estrogen receptor 1 (ESR1), upregulate the expression of SLC3A2 protein, and promote *C. maltaromaticum* colonization in the female gut.

To explore how *C. maltaromaticum* exerts its protective effect against CRC, the authors focused on the synthesis of vitamin D3 by analyzing the gut metabolites and tissue transcriptome profiles of *C. maltaromaticum*-gavaging mice. *In vitro* experiments validated the ability of *C. maltaromaticum* to produce the precursor of vitamin D3, known as 7-dehydrocholesterol (7-DHC). Furthermore, when the culture medium of *C. maltaromaticum* was co-cultured with *Faecalibacterium prausnitzii (F. prausnitzii)*, it resulted in the production of vitamin D3. The activated vitamin D3 then stimulated the vitamin D receptor (VDR), facilitating its nuclear translocation, upregulating *CAMP*, and exerting anti-cancer effects. Finally, the dependence of the anti-cancer effect of *C. maltaromaticum* on VDR was confirmed through experiments involving VDR inhibitors and VDR-knockout cell lines. Li and colleagues' work provides an explanation for the lower risk of CRC in women and demonstrates a mechanism in which estrogen alters the gut microbiota to reduce the incidence of CRC in mice.

This article has several strengths. First, it reveals the mechanism by which gender differences, through the gut microbiota, affect the metabolism of vitamin D3 and subsequently regulate the occurrence of CRC. In the future of precision medicine, this finding may lead to the discovery of female-specific CRC biomarkers and may also lay the groundwork for the potential development of gender-specific probiotics. Secondly, previous studies investigating the "environmental factors-gut microbiota-disease phenotype" mechanism have primarily focused on phenotype differences and correlation analysis, with limited exploration of

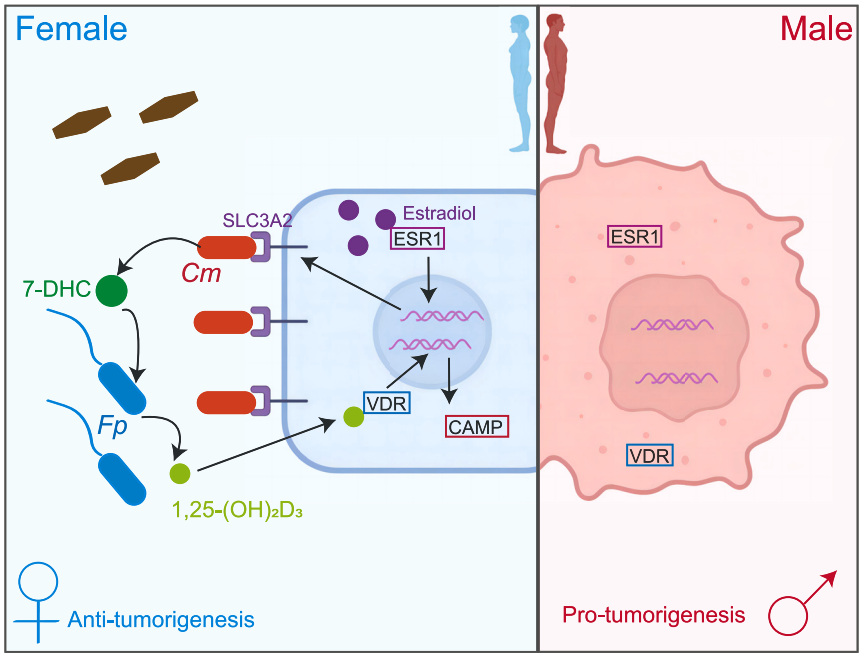

Figure 1. Estrogen prevents colorectal cancer in women through modulation of the gut microbiota

Li et al. proposed a mechanism for estrogen-mediated prevention of CRC in women. Estrogen activates the estrogen receptor ESR1, leading to the upregulation of the transmembrane protein SLC3A2 on the surface of colonic epithelial cells. SLC3A2 interacts with the surface DD-CPase of *C. maltaromaticum*, facilitating the colonization of *C. maltaromaticum* in the female gut. *C. maltaromaticum* can produce 7-DHC, and *F. prausnitzii* utilizes 7-DHC to generate vitamin D3. Vitamin D3 binds to the VDR in epithelial cells, promoting nuclear translocation and upregulation of *CAMP*, which exerts anti-CRC effects.

the impact of upstream environmental factors on the gut microbiota. The innovation of this article lies in the specific elucidation of how upstream estrogen upregulates the SLC3A2 protein, increasing the contact between colonic epithelial cells and *C. maltaromaticum*, thereby enhancing the phenomenon of gender-specific colonization. It demonstrates a paradigm of "host-regulated gut microbiota, which in turn influences the host's disease phenotype." Simultaneously, the discovery of the synergistic symbiosis between *C. maltaromaticum* and *F. prausnitzii*, as well as the production of vitamin D3 by the cross-feeding of *F. prausnitzii* in the culture medium of *C. maltaromaticum*, is equally impressive. It differs from the previous research pattern of a single microorganism encoding enzymes to produce metabolites that affect the host's disease phenotype. Considering the complexity of the gut microbiota and the interactions between different gut bacteria, the authors of this article propose a microbial research paradigm similar to intracellular signaling pathways. The researchers identified a pathway named "*C. maltaromaticum*/7-DHC/*F. prausnitzii*/Vitamin D3," in which *C. maltaromaticum* synthesizes the precursor 7-DHC. Subsequently, *F. prausnitzii* metabolizes 7-DHC into the anti-cancer vitamin D3. This discovery highlights the intricate nature of the gut microbiota, showcasing the synergistic interactions among different bacterial species that collectively impact the host's homeostasis. Importantly, the findings of this study extend beyond female CRC and have broader implications. The findings of Li et al. provide confirmation that estrogen can enhance the abundance of *C. maltaromaticum* in the gut and promote vitamin D3 production. This discovery sheds light on the potential mechanism of osteoporosis in postmenopausal women and offers a theoretical foundation for clinical applications, such as estrogen replacement therapy to elevate serum vitamin D3 levels.[8]

On the other hand, although this article explains the gender differences in CRC incidence from the perspective of the protective effect of estrogen, a recent article published in *Nature* explains this clinical phenomenon from the perspective of risk factors associated with the male Y chromosome.[9] Furthermore, previous studies based on intestinal tumor models have suggested that the gender disparity in CRC are mainly attributed to the promoting effect of testosterone rather than the protective effect of estrogen.[10] In the future, collaborations and discussions among scholars from various research teams, each approaching the same clinical question from unique perspectives, will enhance our comprehension of the intricate and diverse mechanisms underlying diseases. Furthermore, it would be valuable to investigate whether sex hormone-related variations in gut microbiota also impact the pathogenic mechanisms of other diseases characterized by gender-specific risk, such as autoimmune diseases, or hormone-related diseases such as prostate cancer, breast cancer, and endometrial cancer.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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The winner takes it all: Competition drives clonal selection in gliomagenesis

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The exact mechanisms that govern clonal dynamics and selection during early tumorigenesis remain largely elusive. Ceresa et al. provide experimental and mathematical evidence that MYC-dependent competition between individual clones is one driving force of brain tumor evolution, adding a winner/loser aspect to the picture that complements existing concepts.

Competition or collaboration: which of the two is in place, and which is leading to more successful outcomes? This is a fundamental question of life and in multiple scientific disciplines, including cancer research. In cancer, this question has implications for basic mechanisms of disease initiation and progression but also for development of new therapies. On the one hand, recent applications of game theory point toward benefits from collaboration from various cell types in a given tumor, both by subclonal tumor cell populations and with nonmalignant cells, resulting in improved overall fitness of the "tumor organism."[1] This is supported by recent findings from glioblastoma, the most malignant glioma type, where collective self-repair of tumor cell networks occurs[2] and where distinct (while plastic) tumor cell subpopulations collaborate in brain colonization,[3] multicellular network activation, and resistance.[4] On the other hand, it is possible that the competition between cells observed in many biological systems also applies to cancer, with a molecular machinery of relatively higher expression of factors that determine winner/loser interactions, which can be hijacked by evolving cancer cell populations.[5] In this scenario, inter-clonal competition and cancer-microenvironment competition might support the ability of a tumor to progress from the initial stages to organ colonization.[5] In glioblastoma, few and characteristic genetic alterations are acquired early on and thus are present in all tumor cells (clonal), most however in cancer cell subpopulations (subclonal)[6]—but the currently available clinical data from established tumors, even if collected longitudinally, made it impossible to draw definite conclusions about competition vs. collaboration vs. simple co-existence of distinct clones during tumor evolution.

In this issue of *Cancer Cell*, Ceresa et al.[7] made use of an established mouse model of gliomagenesis where PDGF-B is retrovirally expressed, most likely in PDGFRalpha-positive neural progenitors, resulting in molecularly quite homogeneous brain tumors that histologically resemble human glioblastomas, but partially also oligodendrogliomas, evolving over time from lower-grade to higher-grade lesions. Their innovative approach was to include a unique genetic barcode into this oncogenic vector. After confirmation of even distribution of the barcode library and sufficient sensitivity of the method, the authors confirmed that more than 10,000 barcodes were detectable shortly after injection in mouse embryos, reflecting a high number of successfully transduced cells, without overrepresentation of specific barcodes. Importantly, when investigating mice that became symptomatic with neurological symptoms over time, the authors found that the number of main clones dramatically decreased during tumor progression, from a maximum of 495 clones in a 33-day-old mouse to only one detectable single clone in three mice sacrificed between 151 and 342 days after birth. Moreover, a tumor cell mix from established but still oligoclonal gliomas was transplanted into other animals where only one single clone survived over time. Finally, tumor cells from a fully progressed glioma were labeled with genetic barcodes and reimplanted, again with